Appendix 2 - Technical Appendix

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1 Description of model structures and states

The states included in each model capture the possible consequences for a patient with a potentiall inappropriate prescription (PIP) and the typical resource use and increased risks following an event are described. The same model structures were used for both the PIP and non-PIP scenarios, with the only differences being transition probabilities and cost of the PIP or non-PIP treatment.

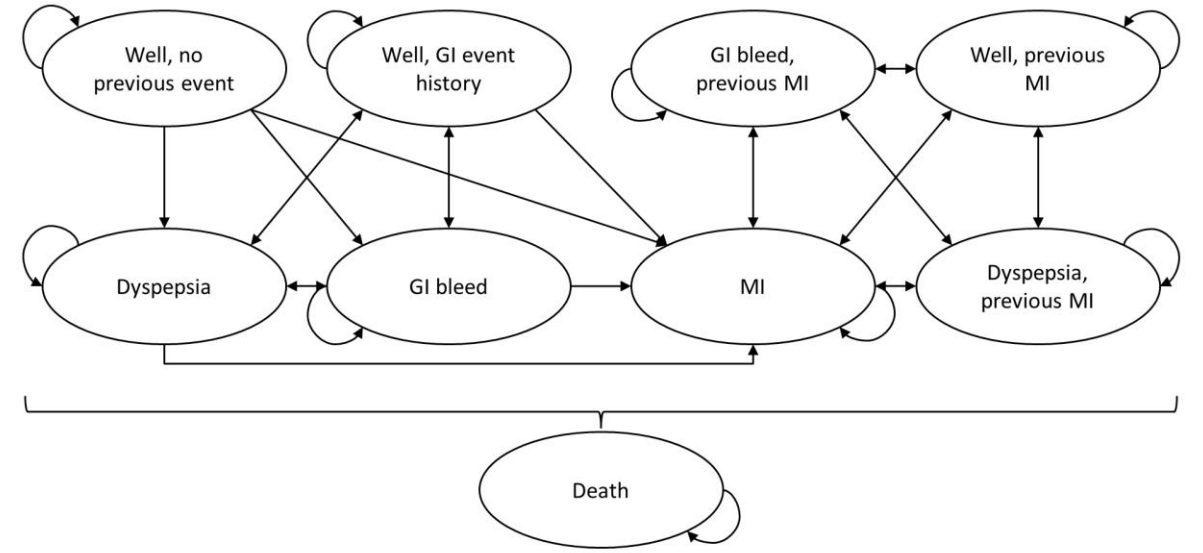
1.1 NSAID model

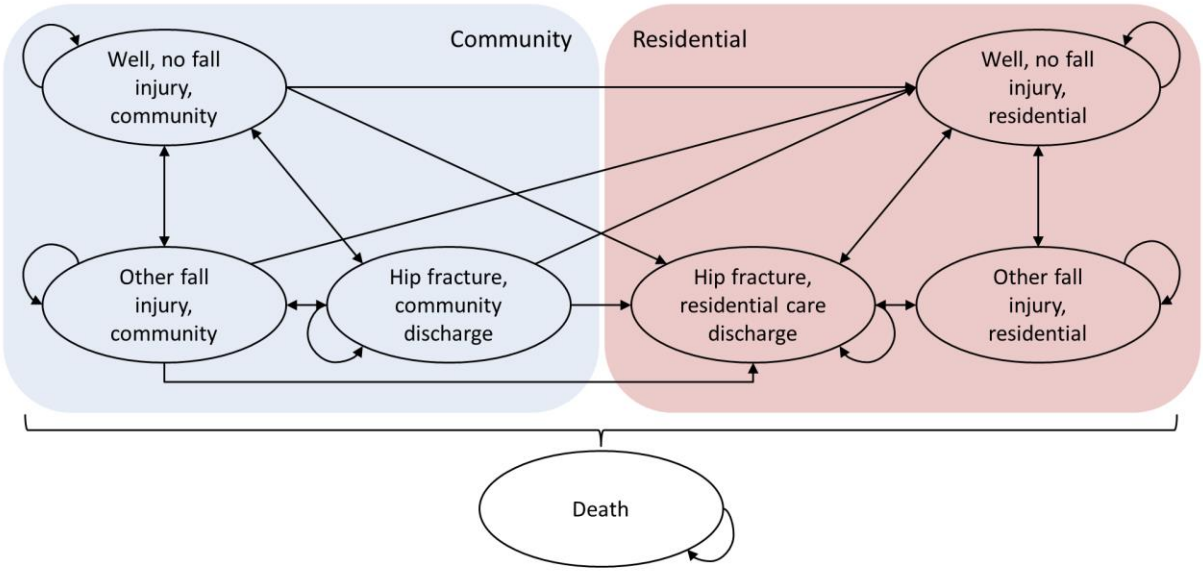
All patients start in the 'Well (no previous event)' state and remain here until they have a gastrointestinal (GI) event (dyspepsia or GI bleed), a myocardial infarction (MI), or die (top, Figure A 1). Patients are on diclofenac 75mg twice daily in the PIP arm or paracetamol 1,000mg four times daily in the non-PIP arm. In the non-PIP arm, the transition probabilities reflect the rates of the adverse events in the general non-steroidal anti-inflammatory drug (NSAID) non-user population, and in the PIP arm, the relative risk in NSAID users was applied to these probabilities.

Patients can transition to the 'Dyspepsia' state where individuals have persistent dyspepsia causing GI discomfort requiring consultation with a doctor and so they attend their general practitioner (GP) for an extra visit, are switched from diclofenac to paracetamol and receive a prescription for a proton pump inhibitor (lansoprazole 15mg once daily for four weeks). They return to the baseline (non-PIP) risk of further dyspepsia and if no further event occurs in the following cycle, they transition to the 'Well, GI event history' state.

Patients who transition to the 'GI bleed' state in this state attend the emergency department (ED), are admitted to hospital for investigation and management of upper GI bleeding, are switched from diclofenac to paracetamol and receive a prescription for lansoprazole 15mg once daily for four weeks. After discharge, they are expected to have additional healthcare use as a result of their GI bleed, namely two GP visits and two outpatient department (OPD) visits.[1,2] As with dyspepsia, they return to baseline risk of a further GI bleed and transition to the 'Well, GI event history' state if they have no further event in the following cycle. In the 'Well, GI event history' state, patients' therapy has been switched from diclofenac to paracetamol, so the cost of medication (paracetamol) and transition probabilities for further GI events or an MI from this state is equal in both the PIP and non-PIP arms.

Patients transition to the 'MI' state following an MI and remain here for one cycle unless they have a further MI in the following cycle. Patients who have an MI incur inpatient treatment costs, are switched from diclofenac to paracetamol and commence medications for secondary cardiovascular prevention. They also have an additional 11 OPD visits and attend their GP an extra 8 times in the





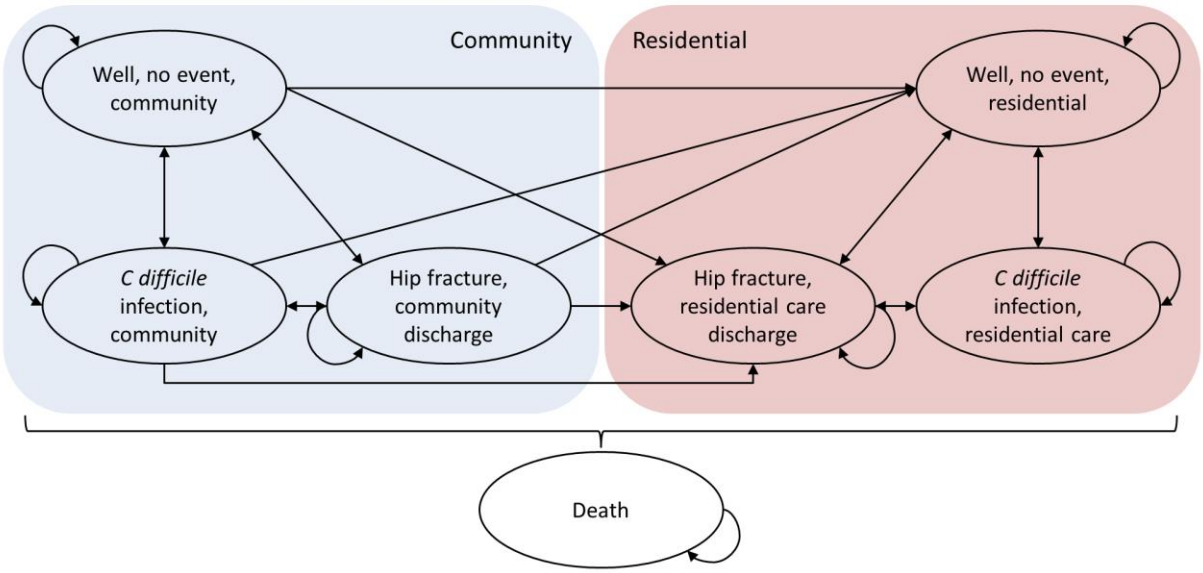


Figure A 1 Structures for NSAID (top), benzodiazepine (middle), and PPI (bottom) Markov models

year of an MI.[3] During this year patients are also at increased risk of a further MI.[4] If no event occurs in the subsequent cycle then patients transition to the 'Well, previous MI' state, where the probability of a subsequent MI falls, although it remains higher than in patients with no previous MI.[4] Patients in any 'previous MI' state incur the costs of attending two extra OPD appointments and two GP appointments per year,[3] as well as the cost of secondary preventive medicines and paracetamol.

1.2 Benzodiazepine model

All patients start in the 'Well, no fall injury, community' state as the cohort is community-dwelling and are assumed to have had no fall injury in the previous 12 months (middle, Figure A 1). The only cost incurred by patients in this state is the cost of the PIP medication, diazepam 5mg twice daily in the PIP arm, whereas no pharmacotherapy is prescribed in the non-PIP arm. Patients in the PIP arm remain on this medication with its associated cost and increased adverse events risk throughout the model i.e. no therapy switch occurs after an adverse event. From this state, a transition can occur following a hip fracture or some other fall injury that a patient seeks healthcare for. Hip fractures were divided into (i) those where the patient returns home and (ii) those which result in the patient being permanently admitted to a nursing home setting. Other events that can occur independently of falls are death and admission to a nursing home.

On having a hip fracture, patients transition to one of the two hip fracture states, depending on where they are discharged to following this event and remain here for one cycle, unless they suffer a further hip fracture. All hip fracture patients present at an ED, are admitted as inpatients and are discharged either back to the community or to a residential care setting. After discharge, hip fracture patients attend an average of 9 additional OPD appointments and have an excess of 10 visits to their GP.[5] For those discharged to the residential setting, there is the additional cost of nursing home residence. For 12 months following a hip fracture patients are at an increased risk of a further fall due to their recent injurious fall.[6] If they have no hip fracture or other fall injury in the following cycle, they transition back to the 'Well, no fall injury' state (either community or residential) and return to baseline fall risk.

All patients with a fall injury requiring healthcare that is not a hip fracture (such as bruising, soft tissue injuries or other types of fractures) transition to the 'Other fall injury' state. The costs incurred in this state are based on a weighted average of the prevalence of different injury types and typical healthcare use taken from an Irish costing study.[7] Half of patients with other falls injuries have one additional visit to their GP, 22% attend an ED, are not admitted and are referred

to their GP for a follow-up visit. Twenty percent attend ED with a non-hip fracture, are admitted as inpatients, and are discharged to community where they have 9 additional OPD visits and 6 extra GP visits.[5] The remaining 8% attend ED with other fall injuries, are admitted as inpatients and following discharge, are referred for one OPD visit and one GP visit for follow-up.[8] The only difference between community and nursing home setting is the additional cost of nursing home residence. As with the hip fracture states, patients remain in this state for one cycle unless they suffer another fall injury and are at an increased risk of a further fall while in this state.

Patients from all of the community-based states transition to the 'Well, no fall injury, residential' state based on the annual probability of being admitted to a nursing home. This background probability of nursing home admission is included as otherwise the number of admissions attributed to hip fracture in benzodiazepine users would be overestimated. Patients also transition to this state in the cycle following a hip fracture which results in permanent nursing home admission, or if they are nursing home residents who suffer a hip fracture or other fall injury. As only permanent admissions are represented in this model, no transitions occur from residential states back to community states.

1.3 PPI model

The model structure (bottom, Figure A 1) is similar to the benzodiazepine model. All individuals start in the 'Well, no event, community' where the only resource use is cost of the PIP or non-PIP medication (i.e. maximal dose proton pump inhibitor (PPI) or maintenance dose PPI). Patients in each arm remain on these medications, with their associated costs and increased adverse events risk, throughout the model i.e. no therapy switch occurs after an adverse event. A number of events can then occur, those that are affected by PIP exposure (*Clostridium difficile* infection and hip fracture) and those that are unaffected (death and admission to a nursing home). Similarly, following a transition to a residential state, patients remain there and no transition back to community can occur.

Following a hip fracture, patients transition to one of the 'Hip fracture' states (again depending on the setting they are discharged to) and remain in this event state for one cycle, unless they suffer a further hip fracture. Regarding healthcare utilisation, the same pattern that applied to this state in the benzodiazepine model was used here, including the additional cost of nursing home care for residential states.

Patients who develop *C. difficile infection* transition to the '*C difficile* infection' state for one cycle where the healthcare resource use is the cost of inpatient management attributable to the

infection, as community-dwelling patients aged 65 years or over are likely to be admitted as a result of an infection.[9] No further healthcare costs are incurred, and there is no increased risk of recurrence following a case (as recurrent cases were included in the baseline probability used) or being in a residential setting.

2 Sources of model inputs

The parameter inputs used in each model, along with the sources for these and the distributions used in the probabilistic sensitivity analysis are provided in Table A 1. The sources of each input are described in more detail below.

2.1 Transition probabilities

2.1.1 NSAID model

The probability of dyspepsia for non-NSAID users and the relative risk associated with NSAID use were taken from a meta-regression of trials and large exposure observational studies.[10,11] In these studies, a hypothesis was stated a priori that the prevalence in trial placebo groups would be lower than in the general population due to a selection bias in trials enrolling healthier patients. Therefore the probability was obtained by applying the relative risk to the prevalence from included NSAID versus NSAID trials. For GI bleeds, a pooled incidence rate in people aged 65 years and over from a review of epidemiological studies was used to calculate the probability.[12] Higher estimates have been reported, however these sources included NSAID users in the study populations. The risk of GI bleeds associated with naproxen and other NSAIDs was taken from a meta-analysis of randomised controlled trials.[13] The same risk of death following a GI bleed was applied to NSAID users and non-users,[14] and a UK hospital based study was the source of age-specific excess mortality estimates.[15] The baseline probability of an MI was estimated from an observational study of NSAID non-users aged 65 years and over and applied to all states with no previous MI,[16] and the probability of a further MI in the 12 months after an event was taken from a recent English population-based study.[4] This study was also the source for the probability of a subsequent MI more than one year post-MI which was applied to the previous MI states.[4] The pooled relative risk of MI on NSAIDs in the PIP arm was taken from the same meta-analysis of trials which yielded the effect on GI bleeds.[13] Probability of death in the year following an MI was taken from a study which provided the cumulative in-hospital and post-discharge mortality rate in a French cohort.[17] The long-term increase in relative mortality post MI was taken from a population-based study and applied to background mortality rate.[4] As this incorporated deaths from further MIs, the mortality from re-infarction was subtracted from this.

The increased risk of dyspepsia, GI bleeds, and MI in the PIP arm only applied to patients in the Well, no previous event state as any transition from this state following an event resulted in a switch from an NSAID to paracetamol. This switch from PIP to the non-PIP option after an adverse event was only applied to the NSAID model, not the benzodiazepine or PPI models. In the former

case patients/doctors may be reluctant to stop the benzodiazepine or it may be felt that stopping would pose a greater risk than continuing in older patients,[18] and for the latter a causal link between PPI exposure and adverse events is unlikely to be made.[19] The impact of relaxing this structural assumption for the NSAID model was assessed in sensitivity analysis.

2.1.2 Benzodiazepine model

This model only concerns falls which result in costs to the health service, therefore falls which result in no injury or falls injury which people do not seek healthcare for were excluded. The probability of a hip fracture was taken from a study reporting number of cases by age group from Irish hospital inpatient data.[7] This source was used in preference to another based on Irish data which provided similar estimates but which were presented separately by sex.[20] The estimate of the proportion of patients who are permanently admitted to a nursing home following hip fracture was taken from a cohort study in Northern Ireland which followed up patients one year post-fracture.[21] For the probability of other fall injuries, the probability of hip fracture was subtracted from the age-specific probability of an injurious fall.[22–25] The same probabilities for hip fracture and other fall injuries were applied to community and residential states. As no trials or meta-analysis of trials have been powered to detect the effect of benzodiazepines on falls, the estimate from the most recent meta-analysis of observational studies was used,[26] and two further meta-analyses had similar results.[27,28] An increased risk of a fracture or other fall injury was applied in the 12 months following a fracture or fall and this effect was taken from a meta-analysis of observational studies which reported the relative risk of a fracture in the year following a fracture.[6] The only attributable mortality included in this model was due to hip fracture,[29,30] and the relative hazard of mortality one year post fracture from a meta-analysis was applied to the all-cause mortality rate.[31] Background age-specific probability of nursing home admission (independent of hip fracture) was calculated from Irish data on the prevalence of nursing home residence.[32]

2.1.3 Proton pump inhibitors model

The probability of hip fracture, the joint probability of being admitted to a nursing home in the 12 months following a hip fracture, the relative mortality hazard in the 12 months following hip fracture, and the probability of admittance to a nursing home independent of hip fracture were taken from the same sources as the benzodiazepine model. The probability of *C. difficile* infection was based on the Irish national clinical guidance which reports the incidence in 2013.[9] The adjusted hazard ratio for mortality following *C. difficile* infection was taken from a propensity score matched-pairs analysis.[33] The source used for the increased risk of hip fracture in the PIP arm

relative to the non-PIP arm was a systematic review and meta-analysis of observational studies,[34] while the dose effects of PPIs on *C. difficile* infection was taken from a single observational study which reported this.[35] The inputs used were the risks in maximal dose PPI users relative to non-users divided by the risks in maintenance dose users relative to PPI non-users. For both fractures and *C. difficile*, there was no evidence of a significant difference between maximal dose and maintenance dose PPI users as reflected by overlapping confidence intervals, and in the case of hip fracture, the Cochran Q test for non-combinability. While this could not be accounted for in the point estimate, this was incorporated into the probabilistic sensitivity analysis when distributions were specified for these estimates.

2.2 Costs

The inpatient cost for managing a GI bleed was taken from the Health Service Executive (HSE) National Casemix Programme Ready Reckoner report which provides the average cost per case for various DRGs for 39 national hospitals participating in the National Casemix Programme.[36] This was consistent with the findings of an Irish study of patients admitted from a hospital ED with low-risk non variceal GI bleeding.[37] A study conducted in a large Irish hospital used a micro-costing approach was the source for the inpatient costs of a myocardial infarction.[38] Inpatient costs for hip fracture were taken from a previous economic evaluation which reported Irish cost data,[20] while for other fall injuries, the cost input was an average of the resource use weighted by the prevalence of different types of injuries, using Irish hospital costs for inpatient stays.[7] No Irish inpatient data was available on costs of *C. difficile* infection however a European systematic review provided several estimates, of which costs from a Northern Irish study were used and the impact of using other estimates from this review were examined in sensitivity analysis.[39,40]

For other healthcare utilisation, the typical excess number of OPD and GP visits post-discharge were taken from published case-control studies for GI bleeds,[1,2] MI (both in the first and in subsequent years post-event), [3] hip and other fractures,[5] and other non-fracture fall injuries.[8] The average cost of an OPD visit was taken from the HSE National Casemix Programme,[36] and cost per GP visit was calculated based on the average annual payment by the health service to GPs per General Medical Services (GMS) patient and the mean number of visits per patient.[41,42] The cost of attending an ED used was the average reported by the National Casemix Programme.[36] Medication costs were calculated using 2014 data from the HSE Primary Care Reimbursement Service (HSE-PCRS) for ingredient costs and a pharmacist dispensing fee of €5 was added for each month's supply to reflect the cost to the health service. As each PIP indicator refers to a drug class,

the medication most frequently prescribed in cases of PIP in a recent Irish population study was used i.e. diclofenac, diazepam and lansoprazole for NSAIDs, benzodiazepines and PPIs respectively.[43] The cost of one year's supply of one defined daily dose (DDD) per day was used. The costs of these PIP and non-PIP medications were varied in one-way sensitivity analyses over the range of costs of different drug molecules. In probabilistic sensitivity analysis, higher variance was included in the distributions for PPI costs as these are subject to continued price reductions through reference pricing.[44] The cost of secondary preventive medications (aspirin 75mg, atenolol 50mg, ramipril 5mg, and simvastatin 20mg) was included for the MI and post-MI states. The annual cost to the health service for a person in nursing home residence was determined from 2014 data on HSE spending on the Nursing Home Support Scheme and the number of individuals funded through this.[45]

2.3 Utilities

The preferences used in weighting for QALYs can be directly measured using rating scale, standard gamble or time trade off (TTO) methods. As these methods can be time-consuming and complex to use, an alternative is multi-attribute utility systems such as the EQ-5D-3L. Firstly, patients describe the health state they are in using a generic descriptive system of attributes which captures all important dimensions of the state. Secondly, valuations for each of these attributes derived from the general public are combined to determine an overall quality for the health state. In the EQ-5D-3L, five attributes are included (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) and for each of these three response levels are defined. A valuation or tariff is estimated for all possible health states (3^5 = 243) by a large sample of individuals valuing each state using the time trade off method. Coefficients are derived for each level of each attribute using regression, which are combined as a decrement from a utility of 1.0 to give a utility for each state.

2.3.1 NSAID model

Disutilities for dyspepsia and GI bleeds were based on directly elicited utilities,[46,47] and the typical period of time patients would suffer symptoms for.[48] This is consistent with previous economic modelling methods,[49] and the disutility was calculated as follows:

$$(1 - utility\ of\ health\ state) \times \frac{Time\ in\ health\ state\ in\ days}{365\ days}$$

The disutility in the year following an MI was taken from a study reporting the annual utility loss associated with various cardiovascular events adjusted for patient characteristics using regression methods.[50] As evidence was conflicting regarding whether there was a long-term quality of life

impact following an MI,[51,52] the most conservative estimate in the literature of MI disutility in subsequent years was applied, and a wide distribution was used in probabilistic sensitivity analysis to reflect the uncertainty around this value.[53]

2.3.2 Benzodiazepine model

The most robust estimates of utility loss following fractures are from two systematic reviews and one Swedish study which uses three different scenarios to analyse the disutility in the 12 months following various fracture types and were similar across these studies.[54–56] The disutility for hip fracture was taken from the systematic review which included the greatest number of studies, and the utility loss in the year following a wrist fracture from this study was applied to the other fall injury state.[56] A disutility was applied to all residential states, consistent with previous economic models relating to hip fractures, on the basis that individuals who are institutionalised are likely to have some impairment in the dimensions captured by the EQ-5D such as mobility, self-care, or usual activities.[57,58] The input used was based on the utility difference between carers of Alzheimer's disease patients in the community and in nursing home residence.[59]

2.3.3 PPI model

The disutility of hip fracture and residence in a nursing home were the same as those used in the benzodiazepine model. The disutility of a case of *C. difficile* does not seem to have been directly elicited in any study using the EQ-5D or time trade off methods. The annual utility loss due to *C. difficile* was based on the utility of being hospitalised and the likely duration of hospital stay, calculated using the equation above.[60,61]

Table A 1 Point estimates for each parameter input and distributions used in probabilistic sensitivity analysis

Parameter description	Value	Distribution	Source
NSAID model			
Transition probabilities			
Probability of dyspepsia in non-NSAID users	0.0497	Beta (4,058, 75,513)	[10,11]
Probability of GI bleed in non-NSAID users	0.0013	Beta (99.71, 76,601.91)	[12,13]
Probability of death following GI bleed by age group		Beta	[64]
60-79	0.11	(156, 1,265)	
80+	0.2	(174, 698)	
Probability of an MI in non-NSAID users	0.0082	Beta (419, 50775)	[16]
Probability of an MI in the 12 months following an MI	0.064	Beta (2339.94, 34221.56)	[4]
Probability of an MI in subsequent years after an MI	0.0143	Beta (1378.65, 95030.28)	[4]
Probability of death following an MI	0.097	Beta (209, 1942)	[17]
Probability of death by age group			
65-69	0.0121		[65]
70-74	0.0198		
75-79	0.0340		
80-84	0.0644		
85+	0.1495		
Effect			
Relative risk of dyspepsia in long-term NSAID users	1.4	Log-normal (0.336, 0.126)	[10,11]
Relative risk of GI bleed in long-term NSAID users	3.07	Log-normal (1.122, 0.114)	[13]
Relative risk of MI in long-term NSAID users	1.53	Log-normal (0.425, 0.174)	[13]
Relative risk of death in people >1 year post-MI	2	Log-normal (0.693, 0.088)	[4]
Utility			
Utility of being in well state		Beta	
65-74	0.77	(129.13, 38.57)	[66]
75+	0.74	(108.51, 38.13)	
Utility decrement in 12m following dyspepsia	0.0325	Gamma (129.13, 38.57)	[46,47,49]
Utility decrement in 12m following GI bleed	0.0433	Gamma (108.51, 38.13)	[46,47,49]
Utility decrement in 12m following MI	0.055	Gamma (74.37, 1352.24)	[50,51]
Annual utility decrement >12m post-MI	0.012	Gamma (4, 333.33)	[51–53]
Costs			
Cost of NSAID treatment	149.64	Gamma (100, 0.668)	[67]
Cost of paracetamol treatment	97.68	Gamma (100, 1.024)	[67]
Cost of managing dyspepsia	152.64	Gamma (100, 0.655)	[67]
Cost of managing a GI bleed	4,983.68	Gamma (44.44, 0.009)	[36,37,67]
Cost of managing an MI	9,856.67	Gamma (100, 0.010)	[3,36,38]
Cost of a previous MI	819.56	Gamma (100, 0.122)	[3,67]
Benzodiazepine model			
Transition probabilities			
Probability of an injurious fall requiring healthcare utilisation			[22–25]
		Beta	
65-79	0.0476	(95, 1,905)	
80+	0.1	(200, 1,800)	
Probability of a hip fracture		Beta	[7]
65-69	0.0014	(197, 140,517)	
70-74	0.0031	(357, 114,804)	
75-79	0.0066	(597, 89,858)	

Parameter description	Value	Distribution	Source
80-84	0.0152	(961, 62,263)	
85+	0.0247	(1,071, 42,289)	
Probability of being in nursing home at 12m following a hip fracture	0.11	Beta (224, 1,810)	[21]
Probability of being admitted to nursing home in general population		Beta	[32]
65-69	0.0021	(301, 143,095)	
70-74	0.0033	(393, 118,759)	
75-79	0.0065	(601, 91,865)	
80-84	0.0151	(980, 63,904)	
85+	0.0241	(1,093, 44,254)	
Effect			
Relative risk of an injurious fall in long-term benzodiazepine users	1.553	Log-normal (0.440, 0.043)	[26]
Relative risk of injurious fall in 12 months post-fall injury	2.0	Log-normal (0.693, 0.039)	[6]
Relative hazard of death in 12 months following a hip fracture relative to people without fracture	3.26	Log-normal (1.182, 0.062)	[31]
Utility			
Utility decrement in 12m following a hip fracture	0.203	Gamma (209.33, 1,031.2)	[55,56]
Utility decrement in 12m following other fall injury	0.06	Gamma (22.13, 368.79)	[55,56]
Utility decrement of being resident in nursing home	0.06	Gamma (0.58, 9.72)	[57–59]
Costs			
Cost of benzodiazepine treatment	77.92	Gamma (100, 1.283)	[67]
Cost of hip fracture	17,394.47	Gamma (385.34, 0.022)	[5,20,67]
Cost of other fall injury	2,782.39	Gamma (25, 0.009)	[5,7,8,67]
Cost of residence in nursing home	42,670.00	Gamma (9,407.98, 0.220)	[45]
PPI model			
Transition probabilities			
Probability of having *C. difficile* infection	0.00358	Beta (1839, 511,848)	[9]
Effect			
Relative risk of hip fracture in maximal dose PPI users relative to non-users	1.462	Log-normal (0.380, 0.097)	[34]
and maintenance dose PPI users relative to non-users	1.247	Log-normal (0.221, 0.050)	
Relative risk of *C. difficile* infection in maximal dose PPI users relative to non-users	2.349	Log-normal (0.854, 0.140)	[35]
and in maintenance dose PPI users relative to non-users	1.735	Log-normal (0.551, 0.114)	
Relative hazard for death in 12m post *C. difficile*	1.23	Log-normal (0.207, 0.089)	[33]
Utility			
Utility decrement in 12m post *C. difficile*	0.026	Gamma (0.530, 20.38)	[60,61,63]
Costs			
Cost of max dose PPI treatment	160.80	Gamma (25, 0.155)	[67]
Cost of maintenance dose PPI	117.12	Gamma (25, 0.213)	[67]
Cost of *C. difficile*	5,837.32	Gamma (19.3, 0.003)	[9,39,40]

3 TreeAge Pro model structures

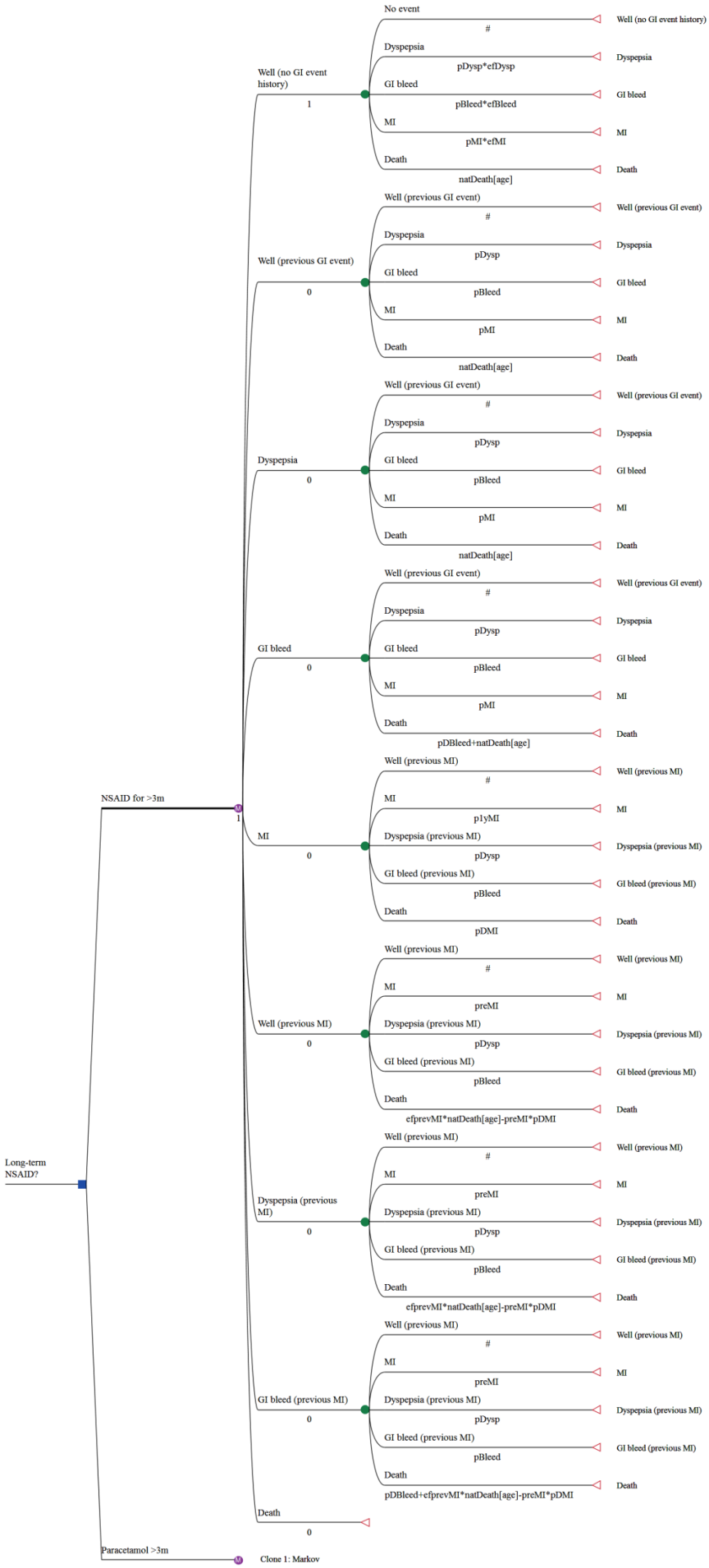


Figure A 2 Decision tree structure for NSAID Markov model in TreeAge Pro

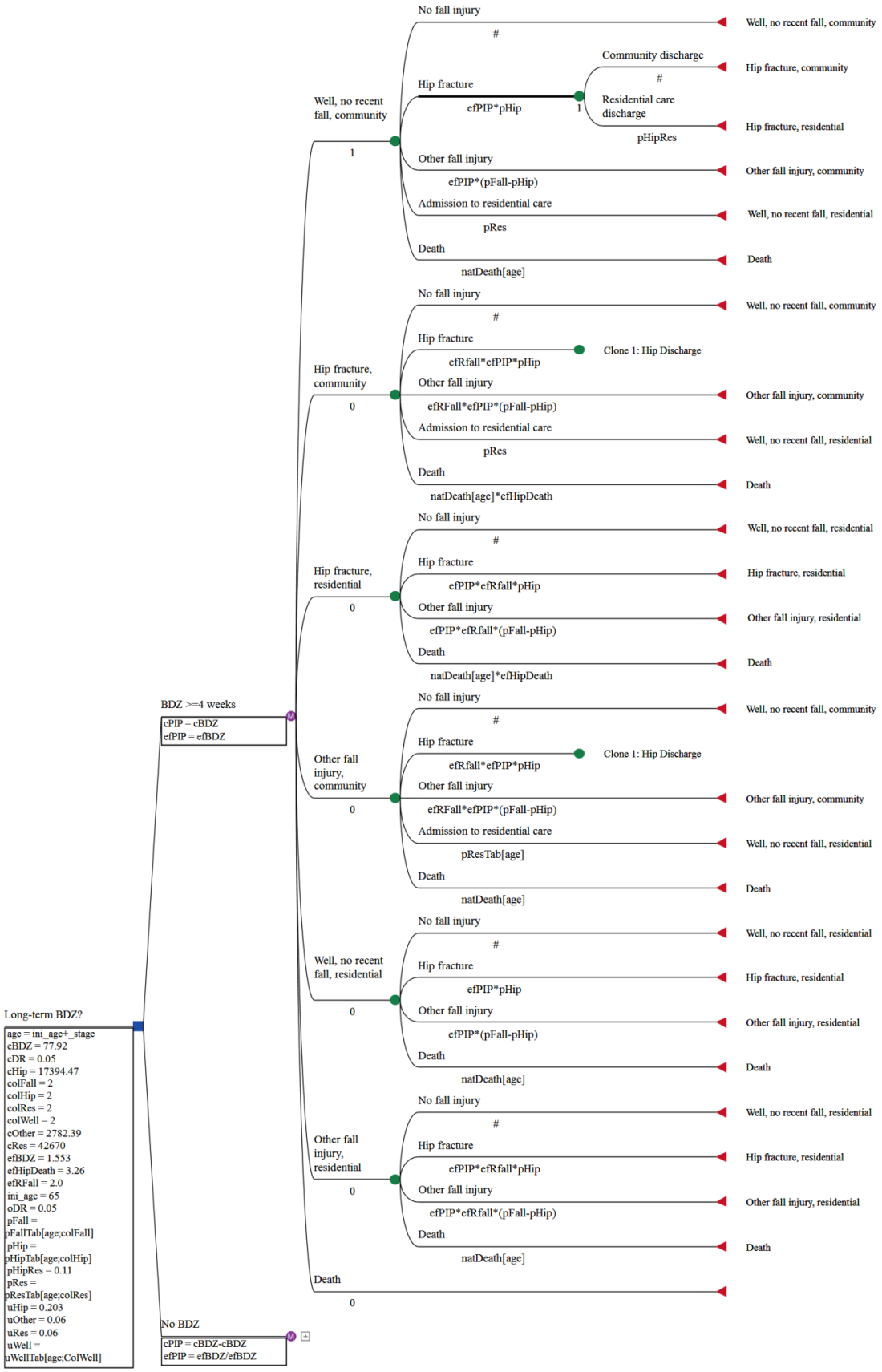


Figure A 3 Decision tree structure for benzodiazepine Markov model in TreeAge Pro

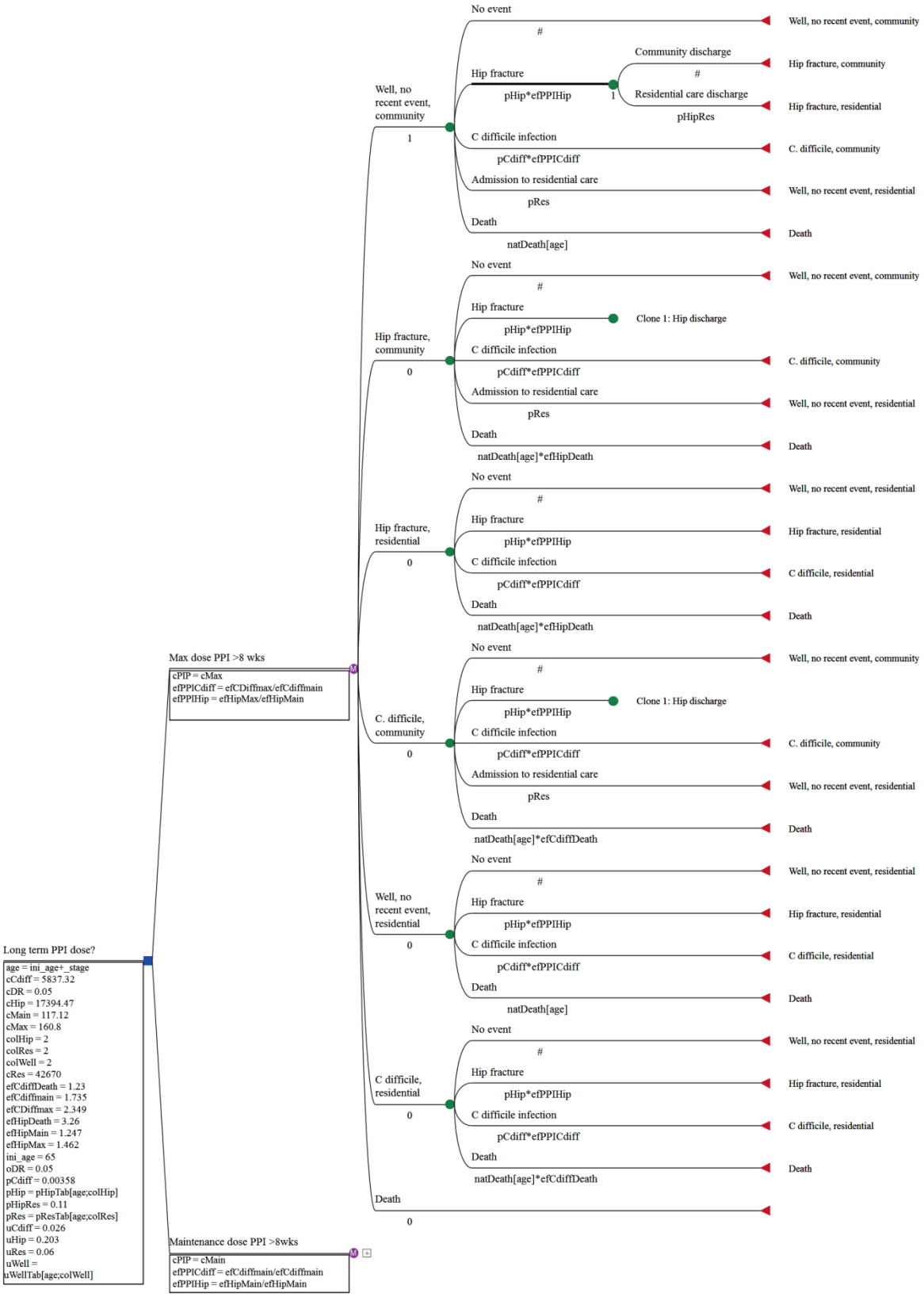


Figure A 4 Decision tree structure for PPI Markov model in TreeAge Pro

4 Probabilistic sensitivity analysis methods

Uncertainty associated with imprecision of the parameter inputs was incorporated into the model using probabilistic sensitivity analysis (PSA) to allow 95% credible intervals (CIs) to be fitted. A distribution of possible values for each parameter was specified, which were fitted under the assumption of a homogenous sample of patients informing parameter estimates (i.e. heterogeneity between patient sub-groups was not investigated). The distribution type used for each parameter reflected the form of data the parameter takes and the standard distributional assumptions used when estimating CIs (as detailed below).[38] The distributions fitted for each parameter were calculated from data available in published sources and these are reported in Table A 1. Each model was run over 10,000 iterations and a random value for each parameter input was sampled from the specified distribution for each run. The outputs of each iteration were recorded to provide a distribution of cost and effect differences and the 2.5th and 97.5th percentiles for these differences were used to estimate 95% CIs. Statistical significance was assumed if the 95% CI for the incremental costs and effects did not include zero. The outputs of each iteration were also plotted on a cost-effectiveness (CE) plane to compare the distribution of ICER estimates for each PIP.

4.1 Approaches used to specify distributions for parameters

4.1.1 Probability parameters

As probabilities can only range between zero and one, the distribution specified must adhere to this limit so that impossible values are not selected from the distribution. A beta distribution is suitable for binomial data as it is constrained between zero and one. It is characterised by two parameters, α and β. In a single study where the number of events and sample size are known, the value of α can be set to the number of events and β to the sample size minus the number of events to specify the beta distribution for uncertainty around the probability point estimate. In the absence of this information, for example if using findings from a meta-analysis, the distribution can be fitted by the method of moments if the mean or proportion and standard error or variance are given, using the following equations:

$$\alpha = \bar{\mu}\left(\frac{\bar{\mu}(1-\bar{\mu})}{s^2} - 1\right),$$

$$\beta = \alpha.\frac{(1-\bar{\mu})}{\bar{\mu}}.$$

4.1.2 Relative risk parameters

Relative risks (RR) are composed of ratios of ratios ranging from zero to infinity and the confidence intervals for which are calculated on the log scale. Therefore, the appropriate distribution for these parameters is lognormal and a distribution can be specified as N(ln[RR], se[ln(RR)]), by taking the natural log of the point estimate and calculating the standard error of this using reported Cis as follows:

$$se[\ln(RR)] = \frac{\ln(Upper\ CI) - \ln(Lower\ CI)}{2 \times 1.96}.$$

4.1.3 Cost parameters

Cost data is constrained to positive values so is generally truncated (to exclude negative values) and right-hand (or positively) skewed as there tends to be small numbers of cases with high costs on the right side of the distribution. Often Poisson or gamma distributions are used to represent cost data, although lognormal distributions can also be used. A gamma distribution can be fitted with the method of moments. For gamma(α,β), the mean ($\bar{\mu}$) is equal to αβ and the variance (s^2) is equal to $\alpha\beta^2$, which can be rearranged to:

$$\alpha = \frac{\bar{\mu}^2}{s^2},$$

$$\beta = \frac{s^2}{\bar{\mu}}.$$

4.1.4 Utility parameters

Utility parameters tend to fall within the range zero to one, however they can technically range into negative values, representing states worse than the reference 'worst health state' used to derive them (usually death). For utilities far from zero, a beta distribution can be used. Another approach is to use the disutility or utility decrement for a health state (1 – utility), which are constrained between zero and positive infinity and can be specified as gamma or lognormal distributions.

In this analysis, we used a beta distribution for the utility in the 'Well' state using the approach outlined in section 3.1.1, and gamma distributions for disutilities using the approach outlined in section 3.1.3.

5 Published estimates of intervention effectiveness

In the OPTI-SCRIPT trial of a complex intervention in general practice, the relative risk of being on a long-term maximal dose PPI post-intervention was 0.45 (i.e. a 55% reduction) compared to usual care.[68] For NSAIDs, a recent trial of education, informatics and incentives in general practice demonstrated a significant reduction of 49.8% in high-risk prescribing relating to NSAIDs and gastroprotection (i.e. a risk reduction of 0.498).[69] A trial to reduce inappropriate prescribing of benzodiazepines using direct patient education demonstrated an additional 23% of those in the intervention group had discontinued benzodiazepines compared to control (i.e. a risk reduction of 0.23).[70]

In the economic evaluation of potential interventions to reduce PIP, a new decision was framed between implementing an intervention to reduce PIP or usual care, as illustrated in Figure A 5 below for NSAIDs. The effectiveness estimate of the published interventions for each type of PIP was used as an input in each analysis as the proportion of patients receiving the intervention who are switched from the PIP drug to the more appropriate alternative.

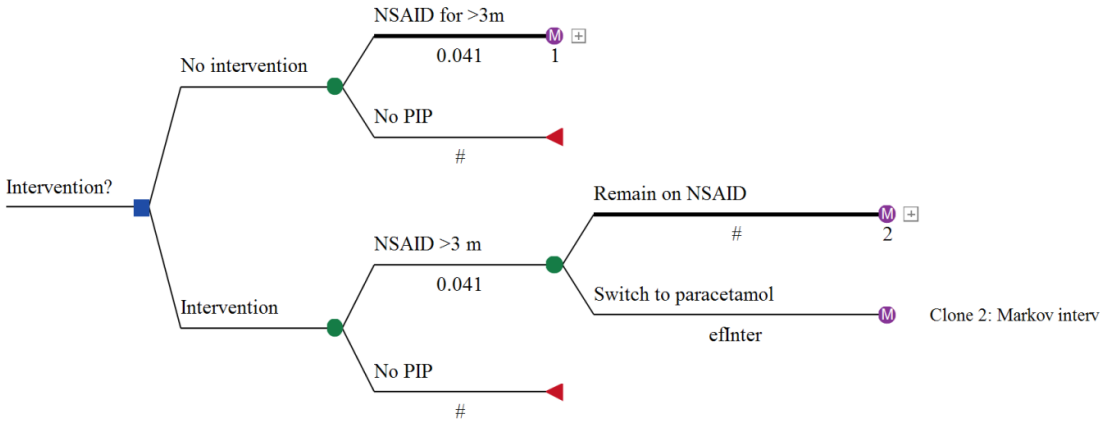


Figure A 5 Decision tree structure of published intervention analysis for NSAIDs

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